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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/747,287	12/22/2000	Beverly Packard	300-948600US	9292

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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 02/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/747,287	PACKARD ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-102* is/are pending in the application.

4a) Of the above claim(s) *1-31,34 and 48-102* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32,33 and 35-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/17/02; 4/7/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group III, claims 32-46, and polypeptide backbone in the Response to the restriction requirement filed August 14, 2003 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Upon examination of claims, it is found that claim 47 should be included in Group III, and claim 34 directed to nucleic acid backbone is withdrawn from consideration, thus claims 32, 33 and 35-47, and the polypeptide backbone joining two identical fluorophores are examined.

Oath/Declaration

2. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. The oath or declaration is defective because the priority documents PCT/US98/03000 and PCT/US00/24882, which are not foreign documents, are listed in the section of claiming foreign priority under 35 U.S.C. 119.

Sequence Listing

3. A paper copy and a CRF of the sequence listing filed November 3, 2003 were found to contain errors, and a copy of Raw Sequence Listing Error Report was faxed to the applicant. During a telephone conversation with Tom Hunter on January 21, 2004, applicant agrees to authorize Examiner to make any necessary changes regarding SEQ ID NO:10 to CRF and paper copy of Sequence Listing (see Letter dated January 28/2004). Therefore, CRF and paper copy of Sequence Listing have been entered.

Informalities

The disclosure is objected to because of the following informalities:

4. The specification recites amino acid sequences (e.g., page 44, lines 9-11; page 69, line 4, DEVD-AFC), however, the sequence identifier "SEQ ID NO:" is not indicated for the cited sequence. Applicant must comply with the requirements of sequence rules (37 CFR 1.821-1.825) to include all the sequences in the sequence listing and to identify each sequence with a "SEQ ID NO:". It is also noted that SEQ ID NOs:220-230, 232-234, 240 and 241 contain B, where B is defined as aminoisobutyric acid in the specification (see page 66, lines 2-3), however, B is described as Asx in the sequence listing, which is Asp or Asn according to Table 3 of MPEP 2422. Therefore, the description of the sequence in the specification is not consistent with the Sequence Listing. Appropriate correction is required.

5. The description of Fig. 5 indicates the DEVD-containing substrate is compound 2 of Example 8, DEVN-containing substrate is compound 3 of Example 8, and ICE substrate is compound 5 of Example 8, however, the compounds are not found in the Example (page 15, lines 19-20). Appropriate correction is required.

6. The specification indicates the compounds listed in Example 8 (compound structures 2 through 13) at page 67, lines 27, however, compounds are not found in the Example. Appropriate correction is required.

7. The specification indicates the peptide of DAIPNleSIPKGY is called NorFES-KGY (page 63, lines 10-15), however, all the compounds in Table 11 use "NorFES" instead of "NorFES-KGY". Appropriate correction is required.

Claim Objections

8. Claims 32 and 40 are objected to because the claim contains recitation of non-elected nucleic acid backbone.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 32, 33 and 35-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mammalian cell comprising a fluorogenic polypeptide such as compounds listed in Tables 11 and 12 comprising a polypeptide backbone joining two identical fluorophores, where the fluorophores form a H-type dimer resulting in the quenching of the fluorescence of the fluorophores, wherein the polypeptide comprising a protease binding site has a defined sequence, and the fluorophore is defined; or a mammalian cell comprising a homolabled peptide protease substrate as shown in the prior art, does not reasonably provide enablement for a mammalian cell comprising a fluorogenic composition comprising a polypeptide backbone joining two identical fluorophores, where the fluorophores form a H-type dimer resulting in the quenching of the fluorescence of the fluorophores, wherein the sequence of the polypeptide and the fluorophore are not defined. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 32, 33 and 35-47 encompass a mammalian cell comprising a fluorogenic composition comprising a polypeptide backbone joining two identical fluorophores, where the fluorophores form a H-type dimer resulting in the quenching of the fluorescence of the fluorophores. The specification however, only discloses cursory conclusions (pages 4-5) without data supporting the findings, which state the present invention provides a cell comprising one or more of fluorogenic indicators, which contain a protease binding site, conformation determining regions and a single species of fluorophore that is capable of self-quenching, where the fluorophores form H-type dimer. There are no indicia that the present application enables the full scope in view of fluorogenic indicators contained in the mammalian cells as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claim is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the absence or presence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claim is broad and encompasses unspecified variants regarding the sequence of polypeptide backbone and the fluorophore in the fluorogenic composition, which is not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

The specification indicates the cleavage rate and percentage of quenching for a series of homo or hetero doubly-labeled NorFES-KGY peptides with different fluorophores (Table 11, Example 5); homo doubly-labeled PAI-2, CS-1 and DEVD-like peptides (Example 6); cellular uptake of various homo doubly-labeled fluorogenic peptides optionally containing additional hydrophobic group (Table 12, Example 7); fluorescence microscopic analysis of cells incubated with elastase or apoptosis-related protease substrates (Example 8); and flow cytometric analysis of cells incubated with apoptosis-related protease substrates (Example 9). However, there are no working examples indicating the make and use of fluorogenic peptides which do not contain the protease binding site but have fluorophores that form an H-dimer.

(3). The state of the prior art and relative skill of those in the art:

The prior art (Packard *et al.*, Proc. Natl. Acad. Sci. 93, 11640-11645, October 1996) teach D-NorFES-D contains carboxytetramethylrhodamine (D) on each side of the cleavage site and is used to monitor the intracellular elastase activity human promyelocyte leukemic cell line HL-60. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the identities of various fluorogenic peptides having fluorescent quenching effect and the use of these peptides in the cell to be considered enabling for variants.

(4). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a mammalian cell comprising a fluorogenic composition comprising a polypeptide backbone joining two identical fluorophores,

where the fluorophores form a H-type dimer resulting in the quenching of the fluorescence of the fluorophores. The specification indicates the cleavage rate and percentage of quenching for a series of homo or hetero doubly-labeled NorFES-KGY peptides with different fluorophores (Table 11, Example 5); homo doubly-labeled PAI-2, CS-1 and DEVD-like peptides (Example 6); cellular uptake of various homo doubly-labeled fluorogenic peptides optionally containing additional hydrophobic group (Table 12, Example 7); fluorescence microscopic analysis of cells incubated with elastase or apoptosis-related protease substrates (Example 8); and flow cytometric analysis of cells incubated with apoptosis-related protease substrates (Example 9). However, there are no working examples indicating the make and use of fluorogenic peptides which do not contain the protease binding site, nor demonstrating how these peptides are cleaved to produce the fluorescent intensity. Even with fluorogenic peptides containing a known protease binding site and two identical fluorophores, the specification indicates some of the fluorogenic peptides do not form productive H-type dimers (e.g., F_1-DEVDGIDPK[F_1]GY (SEQ ID NO:215) and F_1-PDEVDGIDPK[F_1]GY (SEQ ID NO:216), Example 6, page 65, lines 17-20), or do not have sufficient fluorescent quenching (Table 11, F1-NorFES-F1, pages 64, lines 9-12). Since the specification fails to provide sufficient teachings on the identities of various fluorogenic peptides, which do not have protease binding site but have fluorophores that form an H-type dimer, and on how to identify the fluorogenic peptides with a protease binding site and two identical fluorophores that form productive H-type dimers, it is necessary to have additional guidance and to carry out further experimentation to assess the fluorescent quenching effect of a fluorogenic polypeptide.

(5). Predictability or unpredictability of the art:

The claims encompass a mammalian cell comprising a fluorogenic polypeptide comprising a polypeptide backbone joining two identical fluorophores, where the fluorophores form a H-type dimer resulting in the quenching of the fluorescence of the fluorophores, however, the identification of various fluorogenic peptides having fluorescent quenching effects are not sufficiently described in the specification, thus the fluorescent quenching effect of the fluorophores in the fluorogenic peptide is unpredictable, e.g., some of the fluorogenic peptides do not form productive H-type dimers (e.g., F_1-DEVDGIDPK[F_1]GY (SEQ ID NO:215) and F_1-PDEVDGIDPK[F_1]GY (SEQ ID NO:216), Example 6, page 65, lines 17-20), or do not have sufficient fluorescent quenching (Table 11, F1-NorFES-F1, pages 64, lines 9-12).

(6). Nature of the Invention

The scope of the claim includes a mammalian cell comprising a fluorogenic composition comprising a polypeptide backbone joining two identical fluorophores, where the fluorophores form a H-type dimer resulting in the quenching of the fluorescence of the fluorophores, but the specification does not provide sufficient teaching regarding how to identify a fluorogenic polypeptide containing fluorophores that form an H-dimer. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed variants, the teaching in the specification is limited, and the fluorescent quenching effect of fluorogenic peptide is not predictable, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess

the fluorescent quenching effect of the peptide and the use of the peptide in mammalian cells.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 36-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Claims 36, 37 and 38 are indefinite because of the use of the term "Fmoc" or "Fa". The term "Fmoc" or "Fa" renders the claim indefinite, it is not clear what the term means. A fully spelled out word should be indicated in the first occurrence.

12. Claims 38 and 39 recite the limitation "said hydrophobic group" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 39 is also indefinite as to "the amino terminus of the molecule", there is no antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

13. Claims 32, 33, 35, 39, 41, 42 and 43 are rejected under 35 U.S.C. 102(a) as anticipated by Packard *et al.* (Proc. Natl. Acad. Sci. 93, 11640-11645, October 1996).

Packard *et al.* teach an undecapeptide, DAIPNluSIPKGY (named NorFES) is covalently derivatized with carboxytetramethylrhodamine (D) on each side of the cleavage site to form D-NorFES-D, and upon addition of the serine protease elastase, the compound D-NorFES-D is cleaved and an increase in fluorescence intensity is monitored as a measure of protease activity (page 11641, right column, Fig.1); and the absorption spectra of pre- and post-cleaved D-NorFES-D solution indicates the formation of intramolecular ground-state dimers (Fig. 2). The reference also teaches D-NorFES-D is added to human promyelocyte leukemic cell line HL-60 to monitor the intracellular elastase activity (page 11644, Fig. 6: claims 32, 33, 42 and 43). The carboxytetramethylrhodamine, which is also a hydrophobic group, is attached to the α-amino group of aspartic acid of NorFES (page 11640, right column; claims 35 and 39), and the excitation wavelength of the fluorophore is ca. 550 nm (Fig. 2, page 11641, left column; claim 41).

Conclusion

14. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

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February 4, 2004

ROBERT A. WAX
PRIMARY EXAMINER